--22.(amended) The method of claim 15, wherein the administration [comprises] is via intralesional, intramuscular or intravenous injection; infusion; liposome mediated delivery; viral infection; [gene bombardment;] topical, nasal, oral, anal, ocular, cerebro-spinal, or otic delivery.--

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REMARKS

Claims 1-27 were pending. The Examiner withdrew claims 7-14 and 23-27 from consideration. Claims 1, 4, 5, 6, 15, 16, 19, 20 and 22 have been amended to more particularly point out the presently claimed invention. Applicants maintain that such amendments raise no issue of new matter. Thus, claims 1-6 and 15-22 are pending.

Support for "improve" may be found inter alia on page 20, lines 1-5. Support for "inhibit" may be found inter alia on page 36, lines 14-20. Support for "memory loss" may be found inter alia on page 15, lines 1-5; page 41, lines 17-25. Support for "a cAMP-responsive-element-binding-protein-2 to a transcription factor protein or to a DNA required for cAMP-responsive gene expression" may be found inter alia on page 24, lines 30-35; page 27, lines 8-25, and page 28, lines 7-10. Support for "increase cAMP-responsive-gene-expression in the subject" may be found inter alia on page 3, lines 11-12; page 22, lines 12-13.

Election/Restriction

The Examiner acknowledged applicant's election with traverse of Group I, claims 1-6 and 15-22 as reading on a compound that interferes with binding and small molecule (claims 4, 19) in Paper No. 9 filed July 25, 1997. The Examiner stated that the traversal is on the ground(s) that (a) applicant asserts that 35 U.S.C. §121 demands the inventions be examined together due to

an asserted "relatedness" and (b) MPEP §803 is asserted to indicate an undue search burden which demands the inventions be examined together. The Examiner stated that this is not found persuasive because (a) MPEP states that for restriction the invention must be independent or distinct (page 800-3, right column, rev 2, July 1996) and "distinct" is defined as including related subject matters that are patentable over one another (left column, same page) and (b) the restriction requirement was not based solely upon search burden and applicant has not responded to the cited bases for restriction (e.g. 806.05(h)).

The Examiner stated that the requirement is still deemed proper and is therefore made final.

The Examiner stated that claims 2 and 17 of Group I are withdrawn from consideration as non-elected; and that claims 4 and 19 are examined as reading on a small molecule as per Paper No. 9. The Examiner further stated that claims 1, 3-6, 15-16 and 18-22 are examined.

Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1, 3-6, 15-16 and 18-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the recitations of "enhance", repressed", "derepressed," "associated," "interfere," and "interfering" are vague and indefinite. The Examiner further stated that the terms "enhance," "repressed," "derepressed," in claim 1 are relative terms which renders the claim indefinite. The Examiner took the position that the terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not

be reasonable apprised of the scope of the invention.

The Examiner stated that the term "associated," (claim 1, 5, 15) is unclear because is does no sufficiently describe how a protein or DNA as recited is related to cAMP-responsive gene expression, and therefore one of skill in the art would not know what is encompassed by the claim. For example, the Examiner stated, the protein or DNA "associated" with cAMP-responsive gene expression may be indirectly related to cAMP-responsive gene expression or a general housekeeping protein or DNA which affects all gene expression.

The Examiner stated that the terms "interfere," and "interfering," in claims 1 and 15 do not define how binding of the recited protein or DNA is affected by the compound, and therefore one of skill in the art would not know what is encompassed by the claim.

The Examiner stated that the recitations of "binding of the protein or the DNA so as to..." in claim 1, line 8 and claim 15, lines 7-8 are vague and indefinite because the claims do not recite to what the protein or DNA binds, therefore one of skill in the art would no know what is encompassed by the claims.

The Examiner stated that the recitations of "small molecule" in claim 4 and 19 are vague and indefinite because "small" is a relative term which renders the claims indefinite. The Examiner further stated that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The Examiner stated that the recitations of "such binding" in claims 1 and 15 are vague and indefinite because it is not clear what is encompassed by "such binding". For example, the Examiner stated, "such binding" reads not only upon the binding recited

previously in the claims, but also encompasses similar (e.g. not the same) binding.

The Examiner stated that the recitations of "treating" and "treat" in claim 15 are vague and indefinite because it is unknown what constitutes treating or treatment and therefore one of skill in the art would not know what is encompassed by the claim. For example, the Examiner stated, the outcome of treatment is unknown (e.g. complete curing of defect, partial alleviation of symptoms, etc.).

The Examiner stated that the recitation of "gene bombardment" in claims 6 and 22 are vague and indefinite because "gene bombardment" is a laboratory designation and as such may not be standard to all practitioners in the art. It is suggested that "gene bombardment" be accompanied by descriptive nomenclature.

The recitations of "defect" in claim 15 are vague indefinite because it is not known what is encompassed by the term. For example, the Examiner stated, "defect" could refer to a degree of memory loss, the inability to create a memory, incomplete or incorrect memory building, or other.

The Examiner stated that the Markush grouping of claim 16 is improper, and that the listing of conditions comprises conditions which are not themselves not memory defects. For example, the Examiner stated, Alzheimer's Disease is not a memory defect as recited, but is a condition which has as a symptom a memory defect; ischemia is not a memory defect <u>per se</u>, etc.

The Examiner stated that the recitations of "comprises" in claims 20 and 5 are vague and indefinite because it is unclear how a protein can comprise more than a whole functional protein such as those recited in the claims.

The Examiner stated that claims 5, 6, 16, 20, 22 are indefinite in the use of improper Markush language, e.g. "from the group comprising," as this language does not clearly define the members of the group. The Examiner further stated that proper Markush language should recite either "selected from the group consisting of A, B or C" or "selected from A, B or C".

The Examiner stated that the recitation of "capable of altering the phosphorylation" in claims 3 and 18 are vague because it is not known if said altering is necessary to the method, and therefore is not a positive limitation in the claim.

The Examiner stated that the recitations of ApC/EBP and c/EBPß are vague and indefinite because ApC/EBP and c/EBPß are laboratory designations and as such may not be standard to all practitioners in the art. It is suggested that "ApC/EBP and c/EBPß" be accompanied by descriptive nomenclature or SEQ ID No.

In response, applicants respectfully traverse the rejection of claims 1, 3-6, 15-16 and 18-22 under 35 U.S.C. §112, second paragraph. Applicants maintain that the presently claimed invention particularly points out and distinctly claims the subject matter which applicant regards as the present invention. Without conceding the correctness of the Examiner's comments and to accelerate the prosecution of the above-identified application, applicants have amended claims 1, 4, 5, 6, 15, 16, 19, 20 and 22 hereinabove. Applicants maintain that such amendments raise no issue of new matter and address each of the Examiner's statements. Thus, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1, 3-6, 15-16 and 18-22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that the claims are drawn to methods of enhancing long-term memory in a subject which has repressed cAMP-responsive gene expression due to binding of a protein or DNA (associated with cAMP-responsive gene expression) to a CREB-2 by administration of a compound.

However, the Examiner stated, claim 1 does not recite that the subject's cAMP-responsive gene expression, repressed or otherwise, correlates to memory function. The Examiner further stated that the specification is insufficient to direct one of skill in the art to the broadly claimed "subject" of independent claims 1 and 15 in which CREB-2 mediated cAMP-responsive gene expression does correlate with long-term memory, and wherein perturbation of the subject's cAMP-responsive gene expression will effect long-term memory in a predictable manner. The Examiner stated that the state of the art does not support the claimed correlation between the broadly claimed subject's long-term memory with cAMP-responsive gene expression, and in particular CREB-2 mediated cAMP-responsive gene expression.

For example, the Examiner stated, it is clear from the specification and the claims that applicant intends the claims to encompass human subjects with normal memory function and human subjects with memory defects. The Examiner further stated that though the specification exemplifies changes in long-term facilitation in Aplysia (as measured by gill withdrawal reflex coupled with a 5-HT pulse), long term facilitation in Aplysia is

not predictive of more complex memory function in, for example, primates, which are likely to involve multiple systems in the memory process (e.g. Cooper et al., (1991) "The Neurobiological Bases of Neuropharmacology, sixth edition" Oxford University Press, page 443-445, in particular 443 lines 12-16). The Examiner stated that in fact, long term potentiation may not be a completely predictive model of the learning or memory processes in aplysia (e.g. Glanzman, Trends Neurosci. (1995) 18 pages 30-36). The Examiner stated that physiologic and anatomic differences between the CNS of Aplysia and humans further lower the predictive value of the invertebrate model in regard to the broadly claimed subject population. The Examiner further notes that applicant has claimed use of the method in subjects with widely divergent memory defects due to such conditions as Alzheimer's Disease, Parkinson's Disease, head trauma; such conditions have completely different etiologies. The Examiner took the position that one of skill in the art would not predict that the underlying cause for memory defect is the same in these conditions and therefore would not predict efficacious treatment of each to comprise the same methodology(See for example, Cooper et al., (1991), pp 443-445, in particular 444-445, bridging paragraph) Finally the Examiner stated, applicant has not provided a means of identifying suitable subjects commensurate in scope with the claims, wherein said method can be accomplished with a reasonable expectation of success, nor has applicant provided a means commensurate in scope with the claimed subject to assay either the molecular events claimed or the cognitive effect of the method.

The Examiner stated that therefore, the unpredictability of the correlation between the broadly claimed subject's long-term memory with cAMP-responsive gene expression, and in particular CREB-2 mediated cAMP-responsive gene expression, in contrast to single working example provided in the specification combined with the paucity of direction or guidance presented in the

specification and the state of the prior art; one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Additionally, the Examiner stated, the molecular mechanism claimed, both in relation to memory function and on its own, is sufficiently unpredictable that its components render the claims non-enabled. The Examiner further stated that the recitation of "cAMP-responsive gene expression" encompasses a myriad of transcriptional event because cAMP is a ubiquitous second messenger. The Examiner stated that one of skill in the art would not predict that any particular cAMP-responsive transcriptional event would result in the claimed effect on memory. The Examiner stated that in the absence of guidance as to what gene products will predictably affect memory in the broadly claimed subject population, and in the absence of an assay which would identify such gene products commensurate in scope with the claimed subject population and effect, the identification of appropriate transcriptional events within the broadly claimed cAMP-responsive gene expression would require undue experimentation. Likewise, the Examiner stated, the identification of a CREB-2 sensitive protein or DNA which is associated with cAMP-responsive gene expression and predictably affects memory function is unpredictable. The Examiner took the position that though assays for CREB-2 sensitivity and appropriate promoter regions for in vitro transcriptional assays are known, the breadth conferred by the recitation of "a protein or a DNA" leaves open the universe of possible proteins and DNA sequences, which would require undue trial and error experimentation to narrow to the smaller number of functional embodiments.

The Examiner stated that in regard to the broadly claimed compound which interferes with binding, the instant claims have been limited to read upon a small molecule. However, the

Examiner stated, "small molecule" can encompass any molecule which may be considered small, including inorganics as well as peptides, etc., and that in contrast, the specification exemplifies only an antibody with the recited properties of binding interference and effect. The Examiner noted that practitioners in the art do not consider antibodies to be small peptides, but large complex structures, therefore, it is deemed the specification provides no working examples of the claimed compound. The Examiner further stated that generation of an antibody with the recited functional (ability to interfere with binding) and therapeutic characteristics by the claims even more so. The Examiner took the position that applicant has not provided guidance as to what particular compounds of the broadly claimed compounds may function in the claimed method.

The Examiner further noted that dependent claims 3 and 18 are drawn to the compound's ability to alter phosphorylation of CREB-2. The Examiner stated that it is known that CREBs are phosphorylated in multiple locations and that their activity depends upon the particular pattern of phosphorylation. The Examiner stated that as the particular phosphorylation pattern which would be favorable to the recited methods is not known, one of skill in the art would need to determine how phosphorylation correlates with functioning in the instant method without direction from the instant specification or the state of the art.

The Examiner stated that therefore, the unpredictability associated with identification of small molecular compounds with the recited properties, in contrast to the insufficient direction, guidance or working examples commensurate in scope with the claimed compound presented in the specification and the state of the prior art; one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

In response, applicants respectfully traverse the rejection of claims 1, 3-6, 15-16 and 18-22 under 35 U.S.C. §112, first paragraph. Applicants contend that the presently claimed invention is fully enabled by the subject specification. Applicants also maintain that practice of the claimed invention would not require undue experimentation.

Claimed Invention Is Enabled

Applicant's invention is directed to a method to improve long-term memory in a subject whose cAMP-responsive gene expression is decreased which comprises administering to the subject a compound capable of inhibiting binding of a cAMP-responsive-element-binding-protein-2 to a transcription factor protein or to a DNA required for cAMP-responsive gene expression in an amount effective to increase cAMP-responsive gene expression in the subject and thereby improve the subject's long-term memory.

Applicant maintains that the claimed invention is fully described in the specification so that one of skill in the art could make and use the claimed invention without undue experimentation. In support of this contention, applicant points out that the subject specification includes working examples of the claimed invention as well as a sufficient and enabling description. The M.P.E.P. indicates in section 2164.02 that "compliance with the enablement requirement of 35 U.S.C. §112, first paragraph does not turn on whether an example is disclosed." Furthermore, the M.P.E.P. states that "because only an enabling disclosure is required, applicant need not describe all actual embodiments." (Emphasis added.) Applicant points out that working examples are provided in the subject specification and contend that the working examples presented along with the description would allow one skilled in the art to practice the claimed invention without undue experimentation.

Applicant points out the following:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. M.I.T. v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed.Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

See M.P.E.P. §2164.01. Without conceding the correctness of the Examiner's allegations, applicant maintains that experimentation which may be necessary to practice the claimed invention would not be not be undue experimentation. In contrast to the Examiner's position, applicant maintains that the factors to consider in determining whether undue experimentation is required (as listed in M.P.E.P. §2164.01) when taken together indicate that undue experimentation is not required to carry out the claimed invention.

The quantity of experimentation necessary would not be great, since working examples are provided in the experimental details section and that those of skill in the art would routinely exchange the particulars set forth in the working examples to the particulars of other embodiments of the claimed invention. Applicants maintain that the nature of the invention does not change although the particular embodiment may different from that actually reduced to practice.

For example, applicants point out that Figures 5A and 5B show effect of ApCREB2 and ApCREB-1 expression on CRE-Mediated transcription in F9 cells and Figures 7A-10 show a time course of the effect of injection of ApCREB-2 antiserum on short-term and long-term faciliation. Applicants maintain that such disclosures are show that cAMP-responsive-gene expression correlates to memory function. In addition, Example 1 indicates that CREB2 is a repressor for memory via interactions with transcriptional activators necessary for development of long-term

facilitation (see pages 20-21). Example 3 shows that ApCREB2 interacts with ApC/EBP, a protein which is responsive to cAMP, using the yeast two-hybrid system. Indeed, applicants contend that the specification fully enables the claimed subject matter and provides working examples of such.

Thus, applicant maintains the claimed invention is fully enabled by the subject specification and undue experimentation would not be required for one of skill in the art to practice the claimed invention.

In addition, despite the extensive disclosure of experimental details, applicant would like to point out that the Court of Appeals for the Federal Circuit held that the Patent and Trademark Office improperly maintained a utility rejection under 35 U.S.C. §112, first paragraph stating that

> [u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

In re Brana 34 U.S.P.Q.2d 1436, 1442. Accordingly, based on the Brana decision the rejection under 35 U.S.C. §112 must not be maintained. Therefore, clinical trials with human patients must not be required for patentability.

Applicants further respectfully direct the Examiner's attention to the M.P.E.P. §§ 2107.02 (a), Rev. 2, July 1996, for the standard for asserted therapeutic or pharmacological utilities, which states:

> "As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility." (emphasis added).

Moreover, M.P.E.P. §§ 2107.02 (a) further states that:

> "[an] applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. [citation omitted] (emphasis added).

M.P.E.P. §§ 2107.02 (c) clearly states that data from in vitro or animal testing is generally sufficient to support therapeutic utility:

> "If reasonably correlated to the particular therapeutic or pharmacological activity, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound [...]. [...]" (emphasis added).
>
> "Evidence does not have to be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates. Data from any test that applicant reasonably correlates to the asserted utility should be evaluated substantively. [...]" (emphasis added)
>
> "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application." (emphasis added).

M.P.E.P. §§ 2107.02 (d) further states:

> "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human

> clinical trials to establish utility for an invention related to treatment of human disorders [citations omitted] even with respect to situation where no art-recognized models exist for the human disease encompassed by the claims. [citation omitted] [...]"

In summary, applicants maintain that the claimed invention is fully enabled as determined by an analysis of the factors presented in M.P.E.P. §2164.01. In view of the above amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §102 (a or b)

The Examiner rejected claims 1, 3-6, 15-16, and 18-22 under 35 U.S.C. §102 (a or b) as being anticipated by Yin et al., Cell (1995) pages 107-115.

The Examiner stated that Yin et al teach administration of a heat shock activated CREBP-2 (hs-d-CREB2-a), a compound that interferes with CRE binding, to Drosophila via transgenic techniques, and that the reference teaches that activation of the mutant gene increases long term memory.

The Examiner stated that claims 1, 3-6, 15-16, and 18-22 are rejected under 35 U.S.C. §102 (a) as being anticipated by Bartsch et al., Cell 83(6) 1995 pages 979-992. The Examiner stated that Bartsch et al teach the injection of anti-ApCREB2 antibodies into Aplysia sensory neurons, resulting in increased long term facilitation.

In response, applicants respectfully traverse the rejection of claims 1, 3-6, 15-16, and 18-22 under 35 U.S.C. §102 (a or b). Applicants maintain that Bartsch et al. do not anticipate the presently claimed invention. Applicants further maintain that Yin et al. do not anticipate the presently claimed invention.

Yin et al. merely disclose that overexpressing the activating form of Drosophila CREB-1 (dCREB-2a) reduces the number of training trials needed to establish long-term memory in a subject. The Examiner alleges that Yin et al. disclose that hs-dCREB-2 is a compound that interferes with CRE binding. However, there is no such disclosure in Yin et al. Indeed, Yin et al. concede that "we do not yet fully understand the molecular mechanism(s) that contributes to this modulation." See page 111, column 1, last two lines of Yin et al.

Yin et al. do not disclose a method to improve long-term memory in a subject whose cAMP-responsive gene expression is decreased due to binding of a cAMP-response-element-binding-protein-2 to a protein or a DNA required for cAMP-responsive gene expression, or both, which comprises administering to the subject a compound capable of inhibiting the binding in an amount effective to inhibit the binding of the protein or the DNA so as to thereby increase cAMP-responsive gene expression in the subject and improve the subject's long-term memory. Yin et al. do not disclose inhibiting binding of a cAMP-responsive-element-binding -protein-2 to a protein or a DNA. Thus, applicants maintain that Yin et al. do not anticipate the presently claimed invention.

Applicants attach hereto as **Exhibit A** a Declaration of Dusan Bartsch under 37 C.F.R. §1.132. Applicants contend that the Bartsch et al. reference is not a publication by "another" but rather is a publication of applicant's own invention. M.P.E.P. §715.01(c) indicates that a declaration by applicants indicating that applicants are co-inventors and that the others were merely working under the direct supervision is sufficient to remove the publication as a reference. See In re Katz, 687 F.2d 450.

The Declaration sets forth facts as to why the non-applicant, coauthors of the Bartsch et. al. publication are not coinventors

of the subject application. The non-applicant coauthors of the Bartsch et. al. publication were all working under the supervision and direction of Dusan Bartsch in the laboratory of Eric R. Kandel. Accordingly, they are not inventors and Bartsch et. al. is the inventor's publication of their claimed invention less than one year prior to the filing of the subsequent application.

In view of the foregoing, applicants respectfully request the Examiner reconsider and withdraw Bartsch et al. as a reference and the ground of rejection under 35 U.S.C § 102(a) based thereon.

In view of the above amendments and remarks, applicants respectfully request that the Examiner reconsider and remove all grounds of rejection. Applicants earnestly solicit the allowance of the pending claims.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $475.00 extension of time fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents Washington, D.C. 20231

5/11/98
Date

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